EXHIBIT 'A'

results that angiogenesis may be a common pathway for tumor growth and progression. Though several anti-angiogenic agents are being tried to arrest tumor growth, these are not without problems. Since the majority of these agents are proteins/peptides, their long-term use may lead to the development of antibodies which can neutralize their action. These anti-angiogenic substances need to be given repeatedly and some of them are unstable and are difficult to produce in large amounts.

In view of this, it is desirable and necessary to make efforts to stabilize and potentiate the actions of known anti-angiogenic molecules.

The present invention teaches the efficacious use of anti-angiogenic substances, which can inhibit endothelial cell proliferation and coupling them to cis-unsaturated fatty acids, which also have anti-angiogenic and cytotoxic actions on tumor cells, such that the actions of these substances are potentiated by each other. Further, as angiogenesis is involved in other disease processes such as inflammation, tumor metastasis, etc., it is envisaged that the conjugate(s) of anti-angiogenic substances and c-UFAs will be useful in these diseases also.

In this context, it is important to note that the inventor has found that polyunsaturated fatty acids (PUFAs) such as gamma-linolenic acid (GLA), dihomo-GLA (DGLA), arachidonic acid (AA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can selectively kill the tumor cells ((27-32) and under specific conditions and in conjugation with salts such as lithium and a lymphographic agent these fatty acids can actually behave as anti-angiogenic substances, i.e. they block all the blood supply to the tumor and also prevent generation of new blood vessels. Using these fatty acids in this particular combination, the inventor has successfully treated human hepatocellular carcinoma and giant cell tumor of bone with few or no side-effects.

Described hereinafter is a novel combination of a protein and a lipid and method(s) for its use. The protein referred to herein is a potent and specific inhibitor of endothelial proliferation and angiogenesis. The lipid may be one or more of the polyunsaturated fatty acids: LA (linoleic acid), GLA, DGLA, AA, ALA (alpha-linolenic acid), EPA, DHA and cis-parinaric acid. In this instance or method the polyunsaturated fatty acid need to be given only once or at the most twice within a period of 1 to 2 months. This invention teaches

(ii) a lithium salt solution of at least one PUFA chosen from LA, GLA, DGLA, AA, ALA, EPA, DHA; and cis-parinaric acid

(iii) an anti-angiogenic protein/substance which is co-valently linked to the fatty acid or form a mixture (fatty acid + anti-angiogenic protein or peptide).

(d) obtaining second and subsequent radiographic images of the tumor regions after predetermined lapses of time; and comparing the initial radiographic images with the second and subsequent radiographic images to assess the extent of remission of the tumor.

The invention in another aspect resides in a method of causing necrosis in a cancerous tumor by inhibiting blood supply to the tumor, and also by direct cytotoxicity to the tumor cells, comprising the steps of :

(a) locating an artery proximate to the tumor which carries major blood supply to the tumor;

(b) injecting into the located artery a mixture of (i) an anti-angiogenic protein/peptide; (ii) a lithium salt solution of at least one

modulating influence on the actions of anti-cancer drugs.

In the above context, in addition to producing reversal of tumor cell drug resistance by the administration of polyunsaturated fatty acids, it is seen from the invention that the manner of targeting the cancerous tissue is very critical to the efficacy and the speed with which necrosis can be brought about. More particularly, it is realized through this invention that by delivering a chosen admixture of salts of predetermined polyunsaturated fatty acids and predetermined anti-angiogenic substance(s) to the tumor site intra-arterially, intra-venously, subcutaneously, intra-peritoneally or by by direct injection into the tumor bed, a very beneficial and hitherto unknown effect in terms of inhibiting blood supply to the tumor site and inducing tumor cell lysis is achieved simultaneously.

In clinical studies conducted by the inventor with PUFAs, the inhibition of blood supply was pronounced enough to cause cutting off blood supply to the tumor site with very little time lag. In other instances, an unmistaken strangling of blood supply to the tumor region was observed, but was relatively gradual.

One aspect of the invention consists in the preparation of a combination/

Application to mammals: Even though the examples described supra relate to humans, it is envisaged that the method of inhibiting blood supply and using admixture of this invention including an anti-angiogenic substance are equally applicable to other mammals.

Equivalents

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended claims. For example, anti-angiogenic substances referred to herein include not only Angiostatin and Endostatin , platelet factor-4, TNP-470, thalidomide, but other agents with anti-angiogenic capabilities. Also sodium and potassium salts are considered equivalents of each other. Imaging techniques referred to herein are intended to include CAT, MRI, X-rays and other possible imaging methods. Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described specifically herein. Such equivalents are intended to be encompassed in the scope of the appended claims.